REMARKS

1. General Matters

1.1. Claims 17, 85 and 94 have been cancelled, claims 101-102 have been added, and various claims have been amended. In particular, the limitations of claim 94 have been incorporated into claim 90.

1.2. We have addressed all of the claims objections (claims 17, 90, 92, 93, 95, 100) in the manner recommended by the Examiner, except that we refer to the polypeptide of SEQ ID NO:2 in claim 93. SEQ ID NO:1 is a nucleotide sequence.

1.3. Claim 12 previously covered SEQ ID NO:2 per se via 12(a). This has been excised, so (b)-(e) became (a)-(d). SEQ ID NO:2 is still covered by claim 99.

1.4. There is an error in Fig. 3. Two subsequences are labeled "LNR1", and none are labeled "LNR3". The second "LNR1", which is after "LNR2", should of course be "LNR3". Pursuant to 37 CFR 1.121 (d), we submit herewith (1) a corrected Fig. 3 with a header labeled "Replacement Sheet", and (2) a marked-up copy of Fig. 3, showing the correction made, labeled "Annotated Marked-Up Drawing". The correction is that the second "LNR1" has been redesignated as "LNR3".

1.5. There is an important nomenclature problem which has been completely overlooked by us and by the Examiner, and drastically affects the interpretation of the claims.

Claim 12 identifies mature PAPP-A2 as residues 234-1791 of SEQ ID NO:2, consistent with the specification, the figures, and the original sequence listing. (SEQ ID NO:2 is prepro PAPP-A2.)

However, in the sequence listing filed January 11, 2002, the pre-and pro- portions of SEQ ID NO:2 are negatively numbered (as -233 to -1), so the mature sequence is numbered 1-1558. This is consistent with the identification of the coding sequence in SEQ ID NO:1. The same is true for the sequence listing filed January 23, 2003.

Hence we must either (1) conform the specification and claims to the numbering of SEQ ID NO:2 as it appears in the

current sequence listing, or (2) file a substitute sequence listing which restores the original numbering scheme for SEQ ID NO:2 (in which case SEQ ID NO:1 must also be corrected).

37 CFR 1.822(d)(4) says

> The enumeration of amino acids may start at the first amino acid of the first mature protein, with the number 1. When presented, the amino acids preceding the mature protein, e.g., pre-sequences, pro-sequences, pre-pro-sequences and signal sequences, shall have negative numbers, counting backwards starting with the amino acid next to number 1. Otherwise, the enumeration of amino acids shall start at the first amino acid at the amino terminal as number 1.

The word "shall" implies that the numbering scheme used for SEQ ID NO:2 in the January 11, 2002 and January 23, 2003 sequence listings is mandatory. However, MPEP 2423.03 says, "Two alternatives are presented for numbering amino acid sequences. Amino acid sequences may be numbered with respect to the identification of the first amino acid of the first mature protein or with respect to the first amino acid appearing at the amino terminal".

We believe that in view of the pervasive use of the original numbering in the specifications and claims, and in prosecution, that it is better to file a substitute sequence listing, and one is enclosed herewith.

Applicants hereby submit the following:

an amendment to the paper copy of the "Sequence Listing" submitted on January 23, 2003, the amendment being in the form of substitute sheets;

the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein.

The undersigned attorney or agent hereby states as follows:

(a) this submission does not include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is supported by the specification and does not include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is identical to that originally filed [§1.825(d)].

2. Indefiniteness Rejections (OA §§5-10)

Claims 17, 93, 95 and 100 stand rejected for indefiniteness.

2.1. (OA §7). The mature PAPP-A2 sequence is defined at P43, L34 as being AAs 234-1791 of SEQ ID NO:2. The prepro part of PAPP-A2 is defined at P44, L16-17 as being AAs 1-233 of SEQ ID NO:2. Claim 17 has been cancelled. New claim 101 recites amino acids 1-233 directly, without using the "prepro part" terminology.

SEQ ID NO:2 itself is most precisely referred to as a preproPAPP-A2 (P10, L7-8).

2.2. Claim 93 has been amended in accordance with the Examiner's interpretation, i.e., it comprises at least 1169 consecutive amino acids of the "fragment" 234-1791 of SEQ ID NO:2. We don't agree with all of the Examiner's comments in OA §8. Specifically, we don't agree that an 1169 a.a. fragment can be considered 100% identical to a 1558 a.a. protein, even if they are identical in the aligned region.

2.3. In response to OA §9, applicants first note that the positions of consensus sequences LNR1, LNR2, LNR3, SCR1, SCR2, SCR3, SCR4 and SCR5, as well as of the elongated zinc finger

binding consensus sequence, were plainly identified in the original disclosure by P52, L3-10, P57, L17-22, and Fig. 3. We pointed this out in the paragraph bridging pages 11-12 of the last response, and hence there was no justification for the Examiner deeming to give "no patentable weight" to these limitations of claim 95. Since claim 95 was not properly examined, we are requesting that the finality of the September 7, 2004 office action be withdrawn.

As suggested by the Examiner, we have amended claim 95 to identify, for each consensus sequence, its location within SEQ ID NO:2 as determined by reference to Fig. 3.

2.4. OA §10 rejects claim 100 because "processing variant" is allegedly indefinite. The examiner interpreted the processing variants as those "resulting from intracellular proteolysis". Claim 100 has been amended to make this explicit.

3. Written Description

3.1. Claims 90-91, 93 and 95 stand rejected for allegedly failing to comply with the written description requirement.

The Examiner questions four limitations of the claims:

(1) a fragment of at least 6 amino acids of residues 234-1791 of SEQ ID NO:2 (claim 90);

(2) a fusion protein comprising amino acids 234-1791 of SEQ ID NO:2 where said fusion is not a pregnancy associated plasma protein (claim 90);

(3) a fragment of at least 1196 [sic, 1169] consecutive residues of residues 234-1791 of SEQ ID NO:2 (claim 93); and

(4) a consensus sequence labeled LNR-3 (claim 95).

With respect to limitation (1), claim 90 now recites that the fragment is at least 5 amino acids long, for which basis exists at P7, L14. There is also explicit basis for at least 7, 9, 10, 11, 12, 13 or 17 amino acids, see P7, L14-15. At least 17 amino acids is recited in claim 92.

Turning to limitation (2), the proviso that the fusion protein is not a PAPP has been excised. Support for fusion proteins in general appears at P7, L19, P14, L17-22, P15, L29-P16, L10, P17, L27-28.

With regard to limitation (3), P35, L11 recited variants having at least 75% amino acid sequence identity with PAPP-A2. Mature PAPP-A2 totals 1558 residues, and 75% of 1558 is 1168.5, which rounds to 1169. Hence, there is basis for claim 93.

Finally, point (4) complains that LNR3 is not identified in Fig. 3. It was clearly applicants' intent to recognize an LNR3 within Fig. 3 (P52, L6), at a location analogous to the LNR3 region of PAPP-A as identified in Kristensen, et al., 1994, biochemistry, 33, 1592-8 (P52, L4). As pointed out above, LNR3 was mislabeled as "LNR1" in Fig. 3; this has now been corrected.

3.2. Claims 12, 18-19, 75, 83 and 97-99 are also rejected for alleged noncompliance with the written description requirement. It appears that OA §§13-15 reject these claims because (1) of the alternative functional limitations of claim 12, and (2) the lack of any functional limitation claims 97-99.

3.2.1. Taking up claims 97-99, first, these claims related to the prepro part, which does not itself confer any PAPP-A2-like activity. Claims 97-99 have been amended to recite the presence of the mature PAPP-A2 and certain substitution and truncation mutants of same, in a manner paralleling claim 12. Thus, claims 97-99 are drawn to precursors of mature PAPP-A2.

Claims 97-99 have been amended to make this clear.

3.2.2. With regard to claim 12, all of the alternative functions recited in claim 12 are explicitly taught in the original claim 12 of the specification, and hence are considered part of the description. See In re Koller, 613 F.2d 819, 204 USPQ 702 (CCPA 1980).

We have amended claim 12 to make it clear that activities ii) and iii) refer to mature PAPP-A2 (234-1791 of SEQ ID NO:2).

Mature PAPP-A2 (amino acids 234-1791 of SEQ ID NO:2) is representative of

(i) the claimed polypeptides with activity (i),
(ii) the claimed polypeptides with activity (ii), and
(iii) the claimed polypeptides with activity (iii).

For each of these activities the claimed genus falls within the safe haven (at least 95% identity) set forth in the Written Description Training Materials, Example 14.

We would also point out that while there are no other specifically disclosed mutants, there are several specifically disclosed species, notably 234-1791 (mature PAPP-A2, P43, L33-34), the processing variant 200-1791 (P43, L28-31), and the intercysteine fragments disclosed at P26, L32-P27, L2. All of these can be considered specifically disclosed species, and hence the genus is represented by more than one such species.

Enablement (OA §16-18)

Claims 12, 18, 19, 75, 83 and 97-99 stand rejected as having a scope allegedly broader than that of the enabling disclosure. Enablement is conceded for polypeptides comprising SEQ ID NO:2 and for fragments of SEQ ID NO:2.

1. While the Examiner seems to believe that the "and/or" makes the claim more difficult to enable, the reverse is true. The polypeptides which meet the structural limitations of claims 12 et seq. need only meet one of functions (i)-(iii), any one of which is sufficient to confer utility.

2. The person skilled in the art is given considerable guidance as to where PAPP-A2 can and can't be mutated. PP 26-27 imply that knowledge of critical regions on PAPP-A is relevant to design of derivatives of PAPP-A2. The regions most likely to mediate activity are identified by P52, L3-10:

> The sequence motifs of PAPP-A (Kristensen et al., 1994, Biochemistry 33, 1592-8) are also found in PAPP-A2: The catalytic zinc binding motif and residues of the putative Met-turn are underlined and bolded in both sequences. Lin-notch motifs (LNR1-3) and short consensus repeats (SCR-1-5) are boxed. Cysteine residues are shaded. All cysteines

> of mature PAPP-A are also found in PAPP-A2. In addition, the secreted from of PAPP-A2 has four cysteine residues (Cys-343, Cys-533, Cys-618, and Cys-1268) with no counterpart in PAPP-A.

See also P57, L17-22. As to what mutations might be tolerated, there is a detailed discussion of conservative substitution at P39-40.

Even if some polypeptides meeting just the % identity limitation are inoperative, such inoperative mutants are excluded by the activity limitations. See Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989). If, contrary to reasonable expectations, a single conservative substitution in a location outside the taught activity-mediating regions is in fact destructive of functions (i)-(iii), it lies outside the claim.

3. With regard to the claims reciting the signal peptide (97), the propropeptide (98), or the prepropeptide (99), these claims have been amended to further recite mature PAPP-A2 or certain disclosed equivalents. Claims 97-99 are thus directed to precursors of PAPP-A2, and have utility (even if themselves lacking any of functions (i)-(iii) as intermediates in the production of PAPP-A2.

That said, now that claims 97-99 recite the mature PAPP-A2 sequence, they should at the very least encompass one or more linear epitopes of PAPP-A2 and thereby satisfy function (ii). It is by no means impossible that they further satisfy functions (i) and (iii), as fusion proteins comprising an enzyme moiety and a carrier moiety are known to retain the activity of the original enzyme.

In view of the amendment of claims 97-99, the coverage of the preproPAPP-A2 has been excised from claim 12.

4. Prior Art Issues (OA §§19-23)

Claims 12, 18-19, 75, 90-92 and 96 stand rejected as anticipated by Farr. Claims 12 and 90 are independent in form.

4.1. We first analyze 12. The Examiner appears to believe

that Farr's 1624 a.a. PAPP-E polypeptide, aligned with AAs 168-1791 of SEQ ID NO:2 anticipates claim 12 as examined through the combined workings of clauses (e) ("at least 97% identical to ...(b)...") and (b) ("consists of residues 234-1791 of SEQ ID NO:2"). As a result of the present amendment, clause (a) ("comprises SEQ ID NO:2) has been excised (cp. amendments to claim 99) and hence (b)-(e) have been redesignated as (a)-(d). The new nomenclature will be used from now on.

The flaw in the Examiner's reasoning is that she uses an improper method of calculating % identity.

In essence, she calculates % identity as

$$\frac{\text{number of matches}}{\text{length of shorter (PAPP-A2) sequence}} = \frac{1554}{1558} = 99.7\%$$

(The four mismatches are said to be at AAs 447, 846, 1343 and 1739 of SEQ ID NO:2.)

However, this totally ignores that portion of Farr's PAPP-E which corresponds to AAs 168-233 of SEQ ID NO:2.

We believe that percentage identity should be calculated over the length of the <u>longer</u> sequence, with endgaps counted as mismatches. If so, then the % identity is

$$\frac{\text{\# of matches}}{\text{length of longer (PAPP-E) Seq}} = \frac{1554}{1624} = 95.7\%$$

which of course is <u>less</u> than 97%.

We therefore turn to the specification to see what it teaches as to the correct method of calculating % identity.

There is no formal definition of percentage identity, and hence a definition must be inferred. Relevant text includes:

<u>P4, L23-24</u>: "The mature portion of PAPP-A2 is homologous with the mature portion of PAPP-A (approx. 45% identity)."

<u>P9, L31-33</u>: "Homology of PAPP-A2 with PAPP-A is evident upon alignment of the two amino acid sequences as shown in Figure 3. PAPP-A2 and PAPP-A share approximately 45% of their amino acid residues."

<u>P35, L5-9</u>: "In one preferred embodiment of the invention

there is also provided variants of SEQ ID NO:2, and variants of fragments thereof. Variants are determined on the basis of their degree of identity or their homology with a predetermined amino acid sequence, said predetermined amino acid sequence being SEQ ID NO:2, or, when the variant is a fragment, a fragment of SEQ ID NO:2."

We were unable to resolve the intended meaning on the basis of the reference to 45% identity at P4, L23-24 or P9, L31-33, the lengths of PAPP-A and PAPP-A2 being too similar.

Turning to P35, L5-9, if the calculation of degree of identity was intended to use the shorter sequence as the denominator, there would be no need to define "variants of fragments" on the basis of identity with a fragment of SEQ ID NO:2, as then % identity with full-length SEQ ID NO:2 would work just as well.

By the Examiner's logic, any subsequence, however small (even one a.a.) of a longer sequence, however large, would be characterized as having 100% identity to the longer sequence. Moreover, any claim of the form "a peptide comprising a sequence at least X% identical to SEQ ID NO:Y" would be anticipated as all 400 possible dipeptides are known in the art and at least one of them would be a subsequence of SEQ ID NO:Y and thus, by the Examiner's logic, 100% identical to SEQ ID NO:Y.

The polypeptide of 12(a) is necessarily exactly 1,558 residues in length. The polypeptide of 12(b) is necessarily 1538-1557 residues in length. That of 12(c) is 1559-1568 residues in length. If the Examiner agrees with our interpretation of 12(d), then it cannot be shorter then 97% of 1538 (=1492), as the overhang in the aligned 12(b) polypeptide (the longer sequence) would count as mismatches. Nor can it be longer than 1,568 x (1/0.97), which equals 1616, as its overhang relative to 12(c) would count as mismatches, the 12(d) polypeptide then being the longer sequence. Farr's PAPP E is 1624 residues long, and contains four AA-to-AA mismatches, too.

New claim 102 limits the length of the polypeptide of 12(d)

to that contemplated by 12(a)-(c), i.e., the range of 1538 to 1568 residues.

4.2. According to the Examiner, Farr teaches fragments which anticipate claims 90-92 and 96.

Farr's fragments are characterized by the examiner as follows:

	SEQ ID NO:2
SCR-1 (PAPP-E)	1396-1549
SCR-2 (PAPP-E)	1464-1521
SCR-3 (PAPP-E)	1525-1590
SCR-4 (PAPP-E)	1595-1646
SCR-5 (PAPP-E)	1653-1729
LNR-1 (PAPP-E)	586-611
LNR-2 (PAPP-E)	612-644
Zinc-binding motif (PAPP-E)	733-743

Note that by earlier analysis, the mismatches between PAPP-E and PAPP-A2 are at AAs 447, 846, 1343, 1739.

Applicants have amended claim 90 by incorporating the limitations of claim 94, which was not rejected over the prior art. Hence, the rejection of claim 90 is moot.

3. We thank the Examiner for indicating that claim 93, as interpreted, is patentable over the prior art.

5. Allowable Claims (OA §24)

We thank the Examiner for indicating that claims 70, 85, 87 and 94 are allowable if rewritten in independent form. Claim 85 was directed to a polypeptide of claim 12 which comprised mature PAPP-A2. The only such polypeptide was the polypeptide of (a), which comprised preproPAPP-A2 (SEQ ID NO:2). Claim 85 has been cancelled because the coverage of preproPAPP-A2 has been

transferred from claim 12 to claim 99. New claim 101 is directed to SEQ ID NO:2.

Respectfully submitted,

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Enclosures
-Fig. 3 Replacement Sheet
-Fig. 3 Annotated Marked-Up Drawings
-Sequence Listing (paper)
-Sequence Listing (CRF)

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Annotated Marked-Up Drawing

Figure 3 (page 1 of 1)